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Risks and Harms in Psychedelics and Psychedelic-Assisted Therapies

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Care Dimensions

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Disclosures

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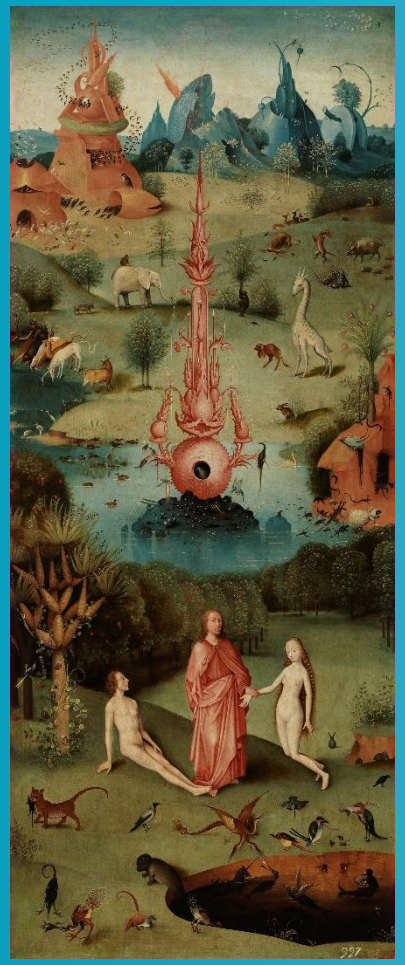
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose

Goals



- Broaden our framework for thinking about risks and harms in psychedelic medicine
- Reflect on the extra-pharmacological factors and therapeutic models that may influence therapeutic benefits versus harms
- Outline broader ethical and sociocultural concerns arising as psychedelics enter the biomedical mainstream

An Anthropological Take

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- Serotonergic psychedelics have been used extensively in diverse cultural settings for millennia as sacrament and for spiritual healing
- Use is often characterized as:
  - Sacred or highly restricted with reverence for psychological effects
  - Ritualized or highly structured with carefully set cultural expectations
  - Communal or highly supported with interpersonal grounding and expert practitioners from the community itself
- These practices— **selectivity, structure,** and **guidance/support**:
  - Likely mitigate adverse psychological reactions
  - Also serve to reinforce cultural worldview and ideology (beliefs, norms, and values) that undergird the social order
- Non-specific amplifiers of **mental** processes
- Value-neutral amplifiers of **cultural** processes
  - Power to alter and reinforce beliefs
  - Transformative human meaning-making canalized by ritual

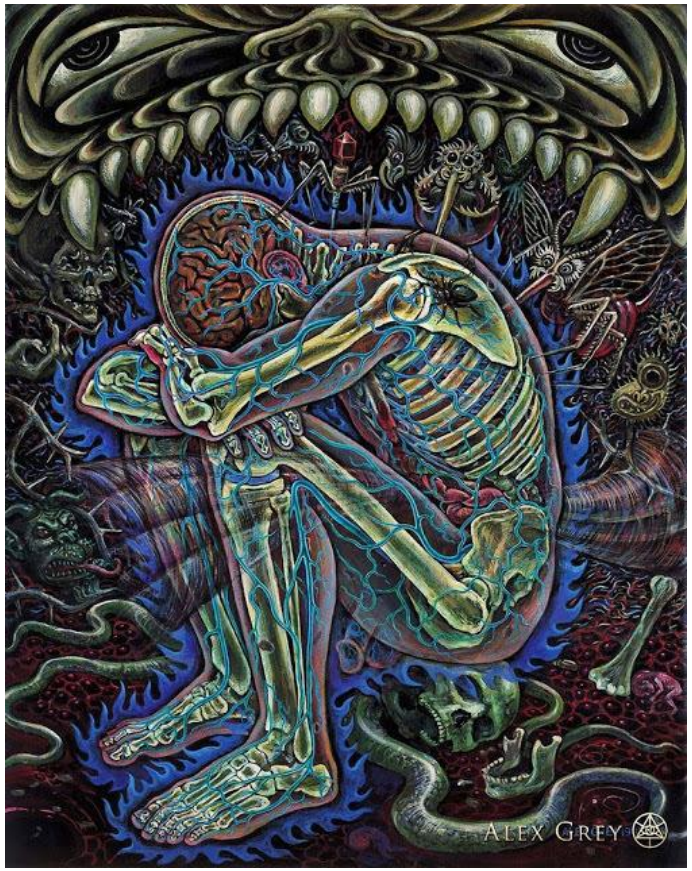
1st Wave: Fast Times For Neuropsychopharmacology

- From 1950 and 1965, an estimated 40,000 patients were prescribed LSD therapy
- Inadequate cultural framework for successful integration into industrialized societies
  - Model Psychosis: Delysid as Psychotomimetic
  - Psycholytic Psychotherapy
- **Selectivity, structure,** and **guidance/support** were overlooked
- Minimal acute physiological adverse reactions:
  - Sympathomimetic
  - Nausea, GI upset, and headache are common
  - Toxicity: no known LD50 for most psychedelic compounds
- No long-term physiological adverse complications:
  - Tachyphylaxis and rapid tolerance
  - No evidence of neurotoxicity or neuropsychological changes from recurrent use

Exceptions include ibogaine-associated cardiotoxicity, ketamine-associated cystitis, and concern for valvular disease due to 5-HT2B agonism with long term microdosing

1st Wave: Fast Times For Neuropsychopharmacology

- Two seminal reviews:
  - Sydney Cohen 1960: questionnaires to 44 of 62 clinician investigators, almost 5,000 patients, estimated 25,000 doses
  - Rick Strassman 1984
- Poor quality evidence from observational and retrospective studies
- Common acute psychological complications:
  - Dysphoria, confusion, anxiety, panic
  - Re-traumatization
  - Transient paranoia, psychosis and dangerous behaviors
  - Short-lived dysphoric reactions, fatigue, irritability, low mood and anxiety
    - ontological shock
    - letdown after the drug-induced hyperphoria and self transcendence
    - Inability to integrate or re-repress released memories
- Challenging Experience Questionnaire
- Primarily viewed as a failure of management due to inadequate **structure** and **guidance/support**



1st Wave: Fast Times For Neuropsychopharmacology

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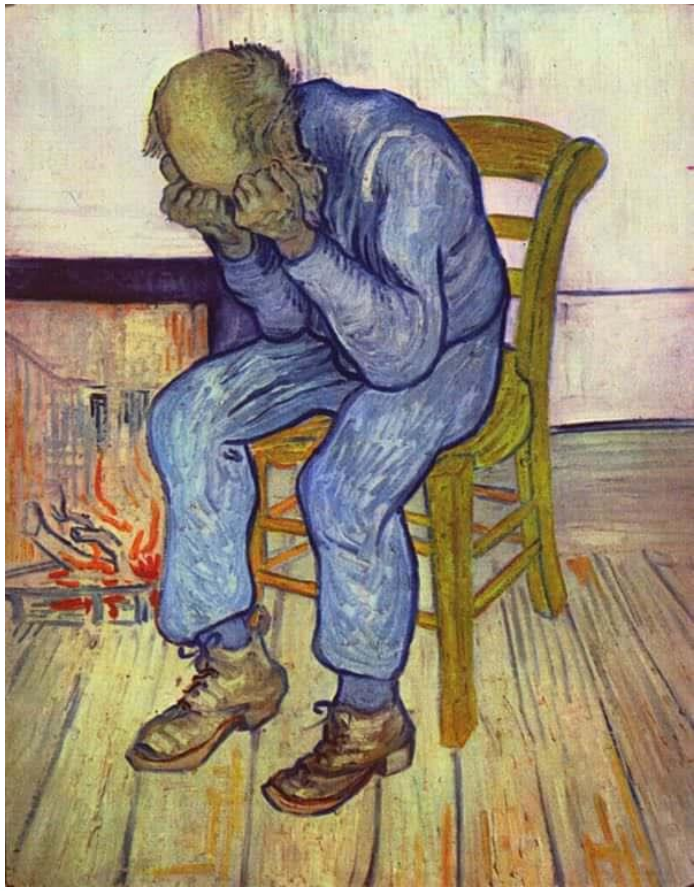
- Long term psychological adverse events/major complications:
  - Recrudescence of LSD-effects weeks or months afterwards
  - Prolonged psychosis
  - Self harm and suicide

	Attempted Suicide	Completed Suicide	Psychotic Reactions
Experimental subjects	0/1000	0/1000	0.8/1000
Patients undergoing therapy	1.2/1000	0.4/1000	1.8/1000

- Major psychological complications in healthy subjects related to:
  - Personal history of severe mental illness, poor baseline adjustment, and underlying personality disorders
  - Strong familial predisposition to schizophrenia
  - Cumulative exposure to psychedelics
  - Use in unsupervised or non-medical settings
  - Polysubstance abuse
- Primarily viewed as a failure of patient selection with inadequate **selectivity**



2nd Wave: Systematic or Syncretic?

- Syncretic clinical practice:
  - **Highly restricted** with small numbers of highly selected patients
  - **Highly structured** with standardized "set and setting" and rigorous research protocol as ritual
  - **Highly supported** with 1-3 dosing sessions, preparation and integration requiring 30-80 specialist clinician hours
- Serious adverse events greatly mitigated by rigorous patient selection and grounding in therapeutic relationship
- Corrective Emotional Experience
  - challenging experiences may be transformed into personally, morally, or spiritually meaningful ones

Flagship Studies: MAPS MDMA Safety Data

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MAPP1: Phase III

- Treatment-Emergent Adverse Events:
  - Common, more prevalent in MDMA study arm
  - Transient
  - Mild-to-moderate in severity
  - Muscle tightness, decreased appetite, nausea, hyperhidrosis, feeling cold, increase in body temperature, tachycardia, and hypertension
- Prevalence of suicidality was reduced in intervention arm compared to baseline and controls

MAPP2: Phase III

- Confirmatory pattern of safety data
- One participant in the MDMA-AT group had the emergence of active suicidal ideation
- No treatment-emergent adverse events of MDMA abuse, misuse, or physical dependence reported in either study

Flagship Studies: Psilocybin Safety Data

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Psilocybin vs. Escitalopram: 59 patients enrolled, 30 received psilocybin

- treatment-emergent adverse events were common
- 87% in psilocybin group (headache) versus 83% in escitalopram group (anxiety and dry mouth)

Single-Dose Psilocybin for TRD COMPASS360: 79 patients received 25mg, 75 received 10mg, 79 received 1mg control

- 14%, 17%, and 9% of participants, respectively, had worsening suicidal state 3 weeks after dosing

Single-Dose Psilocybin for MDD Usona: 51 patients received 25mg, 53 received niacin

- Treatment-emergent adverse events occurred in 83% vs 44%
- Severe adverse events occurred in 8% : migraine, perceptual effects, panic attacks and paranoia
- Residual visual perceptual effects in 6% the day after, but resolved by study conclusion

Pooled Meta-analysis

- Psychiatric symptom worsening in 10% of patients: similar to antidepressant medication
- Compared to 63.6% of patients in waitlist condition reflecting strong “nocebo” effect
- **Substantially protective against risk of symptoms worsening relative to treatment with delayed start**

Meta-Analysis: Adverse Events

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- Clinical studies of classic psychedelics published from 1951 to 2024
- 214 unique studies, only 114 reported AEs (53.3%)
- N=3504
  - 1726 healthy participants
  - 844 inpatient participants, all prior to 1972 (16.5% had a psychotic disorder)
  - 934 outpatient participants
- No cases of sustained psychosis in participants without preexisting psychotic illness
- No cases of *hallucinogen persisting perception disorder* (estimated prevalence of 4.2% among recreational users)
- No completed suicides and only participants with a preexisting depressive disorder developed suicidality requiring psychiatric attention

Hinkle JT, Graziosa M, Nayak SM, Yaden DB (2024) Adverse Events in Studies of Classic Psychedelics: a systematic review and meta-analysis. JAMA Psychiatry online September 4

Long-term Adverse Experiences

- Mixed methods quantitative and qualitative study with 608 participants reporting extended difficulties
- '*Challenging-ness of the trip*' and '*Being in an unguided/uncontrolled setting*' predicted duration
- 73% of respondents reported that the index psychedelic experience was 'unguided'

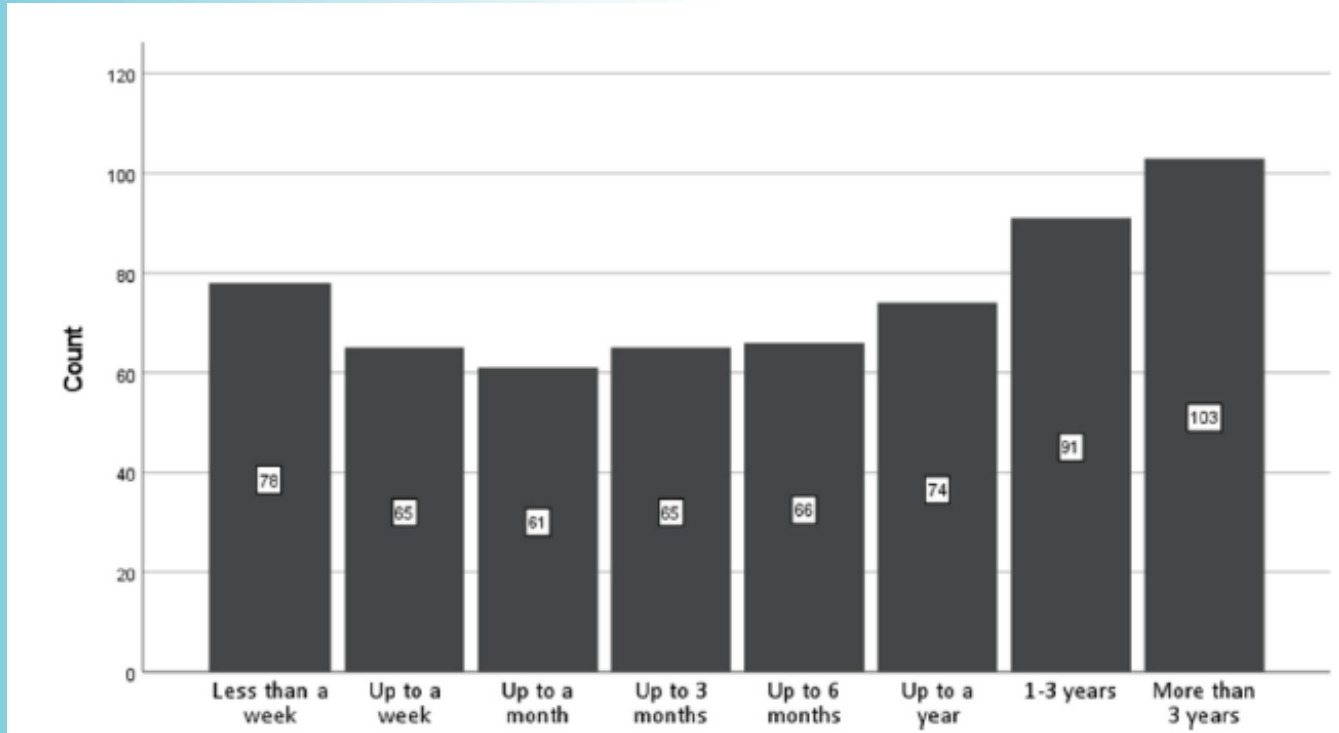

Fig 1. The duration of the difficulties after the psychedelic experience: Response frequencies for duration categories provided.

Evans J, Robinson OC, Argyri EK, Suseelan S, Murphy-Beiner A, McAlpine R, et al (2023) Extended difficulties following the use of psychedelic drugs: A mixed methods study. PLoS ONE 18(10)

Long-term Adverse Experiences

Mixed methods quantitative and qualitative study with 608 participants reporting extended difficulties

"I entered the experience believing that my experience is the literal real external world. The experience contained me living out my worst fears, the deepest possible shame. Other experiences so bizarre and dreamlike I could not make sense of them. These memories left a legacy of confusion about what deeper model of reality to use, and repeated experiences of flipping between these models at different times"

Table 3. Difficulty types (from closed-ended list) reported after the experience ended for at least one day, with frequencies and percentages.

Difficulty Type	Frequency	Percentage
Emotional difficulties (e.g., the way you felt emotionally or the ability you had to emotionally regulate)	464	76
Self-perception difficulties (e.g., the way you felt about or understood yourself)	355	58
Cognitive difficulties (e.g., the way you thought about things)	318	52
Social difficulties (e.g., the way you interacted the related to other people)	316	52
Ontological difficulties (e.g., the way you understood reality and existence)	304	50
Spiritual difficulties (e.g., your spiritual beliefs)	209	34
Perceptual difficulties (e.g., the way your vision or hearing functioned)	156	26
Other Difficulties	125	21

Evans J, Robinson OC, Argyri EK, Suseelan S, Murphy-Beiner A, McAlpine R, et al (2023) Extended difficulties following the use of psychedelic drugs: A mixed methods study. PLoS ONE 18(10)

Long-term Adverse Experiences

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- 90% of respondents agreed that psychedelics can be helpful
- 55% of respondents continue to take psychedelics

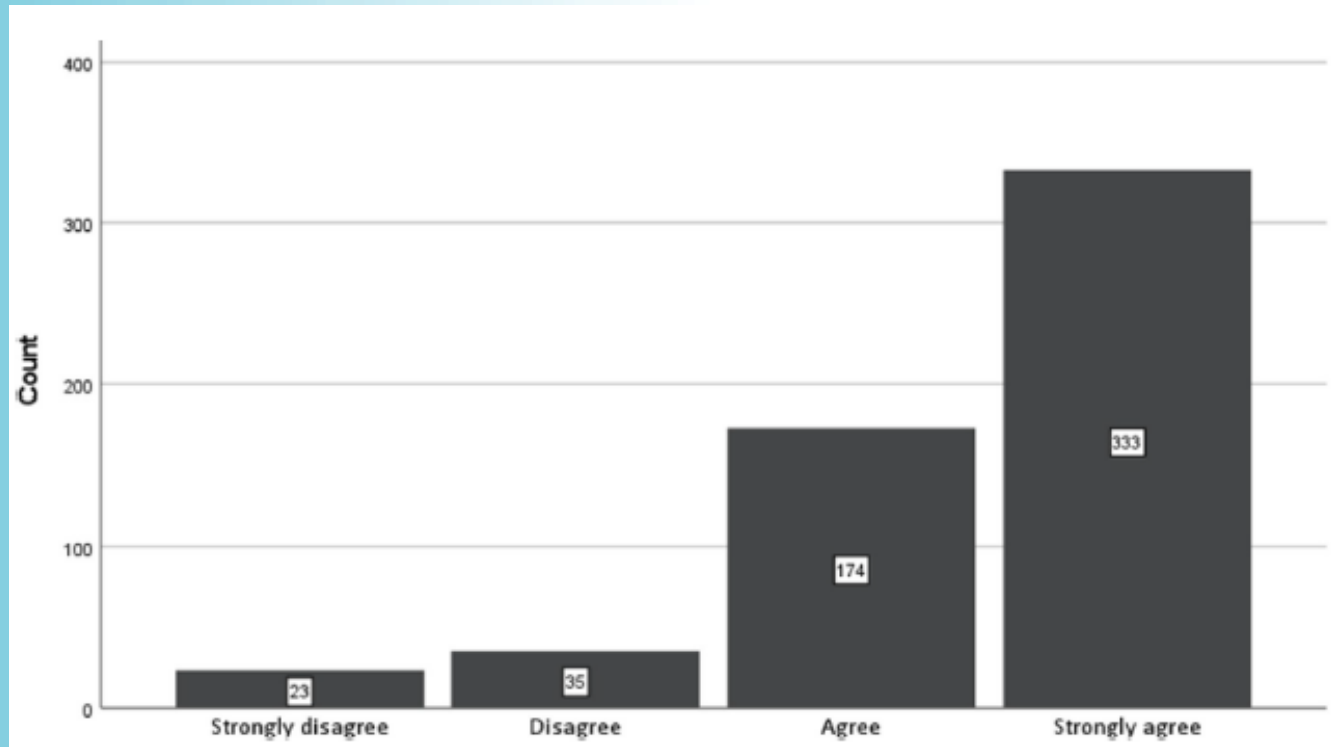

Fig 2. Response frequencies to the question "I believe that the insights and healings gained from psychedelics, when taken in a supportive setting, are worth the risks involved".

Evans J, Robinson OC, Argyri EK, Suseelan S, Murphy-Beiner A, McAlpine R, et al (2023) Extended difficulties following the use of psychedelic drugs: A mixed methods study. PLoS ONE 18(10)

Long-term Adverse Experiences

Mixed methods quantitative and qualitative study with 608 participants reporting extended difficulties

"The man who comes back through the Door in the Wall will never be quite the same as the man who went out.

He will be wiser but less sure, happier but less self-satisfied, humbler in acknowledging his ignorance yet better equipped to understand the relationship between words and things, of systematic reasoning to the unfathomable mystery which it tries, forever vainly, to comprehend"

Aldous Huxley, The Doors of Perception

Evans J, Robinson OC, Argyri EK, Suseelan S, Murphy-Beiner A, McAlpine R, et al (2023) Extended difficulties following the use of psychedelic drugs: A mixed methods study. PLoS ONE 18(10)

Debates in Theory and Praxis

Psychological Support versus Psychotherapy

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Theoretical orientation regarding **brain/mind** in psychology and mental health shifts our frame for considering adverse events and the relationship of psychedelics to psychotherapy

Physicalism: materialist/reductionist

- The drug experience is an epiphenomena independent of and unnecessary for therapeutic efficacy
- Primarily a **pharmacological** intervention
- The role of **psychological support** is primarily to promote **safety** and reduce the incidence and intensity of acute psychological adverse events
- Non-psychoactive psychedelics
- **Good fit** with FDA expectations and current practice models

Humanism: dualist/idealist

- The drug experience drives therapeutic efficacy
- Primarily a **psychotherapeutic** intervention
- The role of **psychotherapy** is primarily to promote **efficacy** through therapeutic relationship and psychodynamic process
- The psychedelic is a catalyst
- **Disrupts** current regulatory and practice models
- Any potential harms of bad/unethical psychotherapy become magnified
- Expanded framework for thinking about potential harms required

Goodwin GM, Malievskaiia E, Fonzo GA, et al (2024) Must psilocybin always “assist psychotherapy”? Am J Psychiatry 181(20-25)

Expanded Adverse Event Framework

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Adverse events not currently included in the MedDRA-V5 that may require additional assessment in psychedelic medicine trials

- **Behavioral AEs:** changes in the vegetative behaviors like sleep, eating, sex, and addictive behaviors not captured in MedDRA
- **Perceptual AEs:** persisting perceptual distortions
- **Psychotherapy-related AEs:** boundary transgressions, undue influence, exploitation
- **Sociocultural AEs:** change and dissonance in emerging worldview
- **Psychospiritual AEs:** existential distress, religious or spiritual struggle
- **Interpersonal AEs:** change in relational style
- **Affective, Cognitive, and Metacognitive AEs:** change in sense of self or self/other boundaries

Palitsky R, Kaplan DM, Perna J et al (2024) A Framework for assessment of adverse events occurring in psychedelic-assisted therapies. J Psychopharm 38(8) 690-700

Psychospiritual Complications

- Release of repressed psychological material with accompanying feelings of shame and guilt
- Ontological shock and insecurity
- Ego-inflation and grandiosity
- Spiritual Bypass
  - *tendency to use spiritual ideas and practices to sidestep or avoid facing unresolved emotional issues, psychological wounds, and unfinished developmental tasks*

Although there are exceptions, people who find that the implications posed by the LSD experience are contrary to their basic philosophies become dysphoric. Invariably, those who take hallucinogenic agents to demonstrate that they have no value to psychiatric exploration have an unhappy time of it.

- Sidney Cohen 1960

Cultural and Ethical Harms

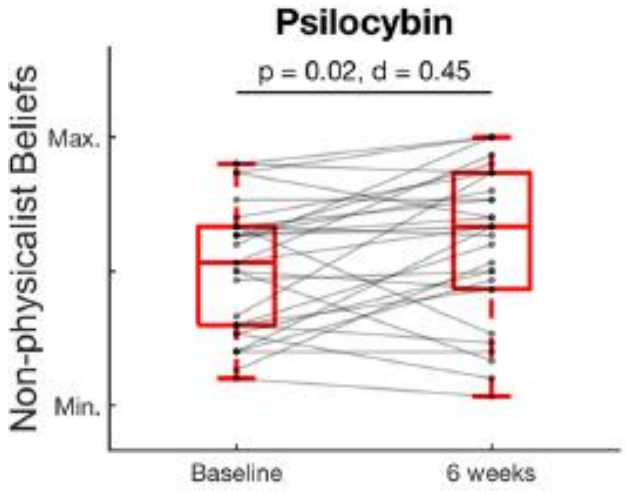
The patient under LSD, from a therapeutic point of view, is quite definitely hyper-suggestible.

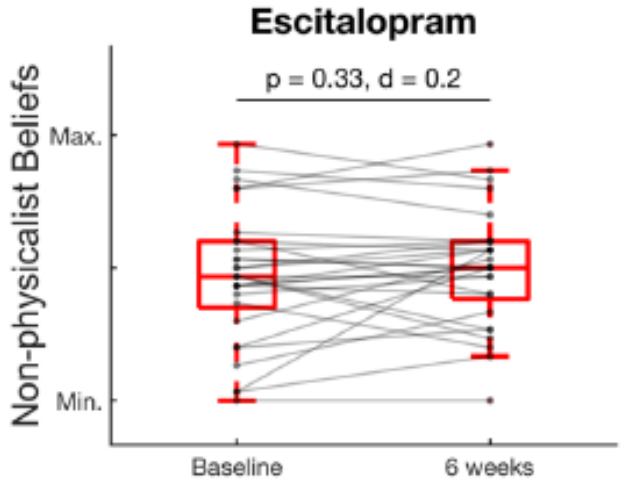
-Josiah Macy and Abramson 1960

- Meaning enhancement and heightened suggestibility
  - Transference and countertransference in the clinical encounter
  - Risk of retraumatization
- Altered ego structure, social behavior and philosophical worldview
- Value-neutral amplifiers of **cultural** processes
  - Power to alter and reinforce beliefs
- The extra-pharmacological factors that structure and contain to ensure safety also prime expectations, imprint the subject, and can shape the vector of cultural change
- A monolithic biomedical model may not be safe or therapeutic for in a culturally diverse society
- Biomedical hegemony may increase harm to culturally marginalized and other vulnerable populations

It is conceivable that LSD may serve as a gratification for the therapist's own needs for power.

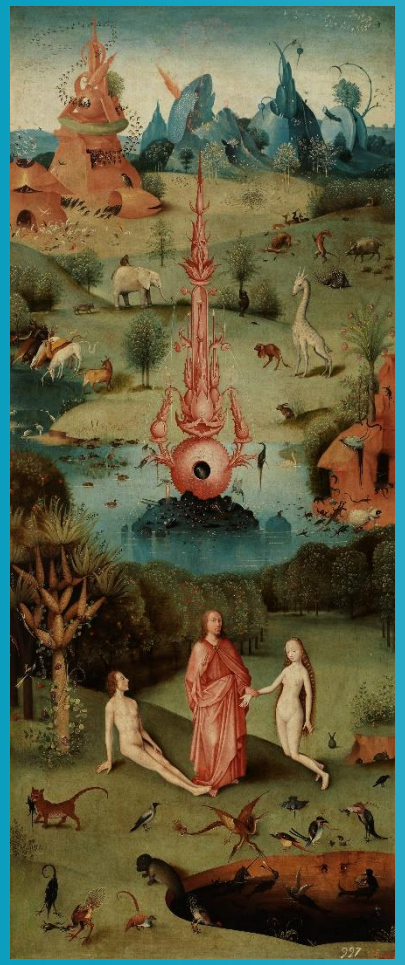
- Sidney Cohen 1960





Timmerman et al (2021) Psychedelics alter metaphysical beliefs. Sci Rep 11:22166

No "Bad Trips"



Euphoria

Mystical Experience

Spiritual Bypass

Escapism

Therapeutic

Pathogenic

Corrective Emotional Experience

Catharsis

Re-Traumatization

Dysphoria

No “Bad Trips”: just bad containers

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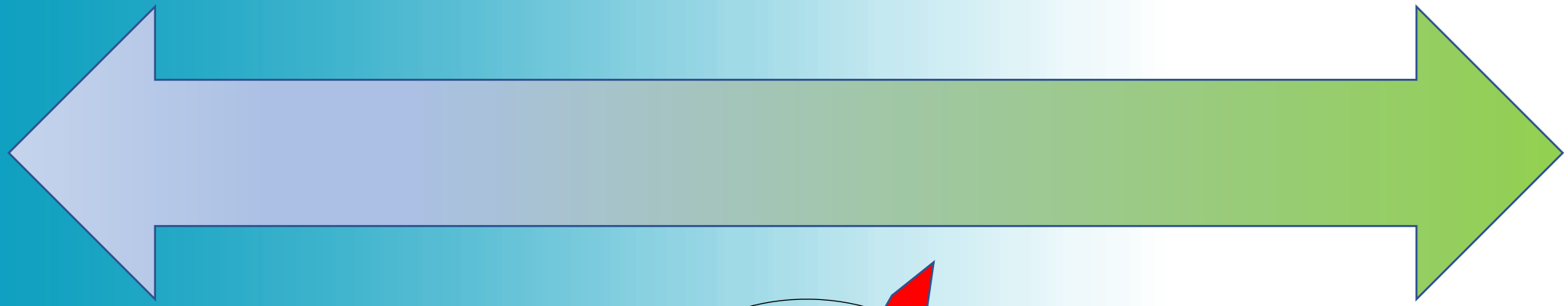


Pathogenic:

Genetic and contextual vulnerability to psychosis

Polypharmacy or dose too large

No meaningful intention

Unrealistic, unmet or negative expectations

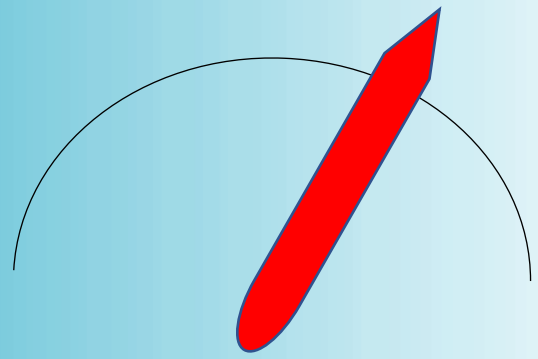
No guide or poorly trained or unethical guides

Chaotic events, before, during or in the afterglow

Disagreeable social or physical environment

Lack of aftercare

More Drug



Extra-Pharmacological Factors

Therapeutic:

Ritual/Structure, Boundaries, and Commitment

Preparation, Intentionality and Positive Expectations

Therapeutic Relationship: before, during, and after

Conducive and coherent environment

Integration…. Integration...Integration

Adjunct mindfulness practice

More Therapy

It is really the mistake of our age.

We think it is enough to discover new things, but we don't realize that knowing more demands a corresponding development of morality.

Jung and Adler 1976

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Conclusions

- Theoretical orientation will inform service design
- The infrastructure we need to deliver this care broadly and safely has not been built yet.
- Issues of cost, access, and inclusivity have the potential to exacerbate rather than alleviate mental health disparities
- We need to continue to innovate new therapeutic models that are more economical, inclusive, and culturally-adapted to meet the needs of diverse populations
- The service models we design to deliver this care will shape individual clinical outcomes, but also transform health care and society at large

Recommended Reading & References

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PATH Trial Research Team

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